NAVAL HEALTH RESEARCH CENTER

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SUMMARY

Problem

Circadian desynchronosis caused by shiftwork or jet lag can have detrimental effects on alertness and performance, which could impair productivity and safety. This can be a chronic problem, since even long-term night-shift workers rarely show complete adjustment of circadian rhythms to the reversed sleep/wake cycle. Circadian desynchronosis can also disturb sleep, which may impair subsequent performance, thereby compounding the problem.

Objective

The purpose of this study was to examine timed bright light exposure and electromagnetic sleep induction (LEET), separately and together, as interventions to improve sleep and performance after a shift of the work/rest cycle.

Approach

Forty-three subjects participated in a study involving a 10-hr phase delay of the work/rest cycle. Subjects were studied for 2 days before and 3 days after the phase shift. Performance was examined with an extensive cognitive performance assessment battery (PAB), sleep was studied by polysomnographic recording (data reported elsewhere), and phase shifting of physiological circadian rhythms was evaluated by recording core body temperature, and urinary 6-sulphatoxymelatonin (6-SM) excretion. Subjects received either bright white light or dim red light from 2200-0200 each night, starting the night of the phase shift. Subjects received either inactive or active LEET therapy for 20 min prior to the daytime sleep periods.

Results

6-SM data indicate that bright light exposure increased the phase delay seen in this circadian rhythm in the 3 days after the work/rest schedule shift. Temperature data appear to have been obscured by activity level related masking effects. The bright light treatment shows evidence of improving accuracy on a broad range of cognitive performance, without compensatory decreases in speed. One task showed decreased accuracy, possibly because the function tested has a performance rhythm out of phase with most other types of cognitive performance. The cognitive performance findings are most consistent with phase shifting effects of bright light rather than direct alerting effects, since no evidence was seen of greater effects during the actual light exposure periods than at other times. LEET administration before the daytime sleep periods showed little evidence of affecting either performance or 6-SM.

Conclusion

After a 10-hr phase delay of the work/rest cycle, bright light timed to promote a phase delay of circadian rhythms speeds up adjustment of physiological circadian rhythms and improves accuracy of several types of cognitive performance during the new work period. LEET does not appear to affect either performance or circadian rhythms.

INTRODUCTION

Circadian desynchronosis caused by shiftwork or jet lag can have detrimental effects on alertness and performance, which could impair productivity and safety (1-4). With jet lag this is ordinarily a temporary problem. However, even long-term night-shift workers rarely show complete adjustment of circadian rhythms to the reversed sleep/wake cycle (5,6). Circadian desynchronosis can also disturb sleep, which may impair subsequent performance, thereby compounding the problem (7,8).

Some interventions may offset problems produced by shiftwork or jet lag, either by speeding up resynchronization to a new sleep/wake schedule, or by improving sleep, with secondary improvement of alertness and performance. Possible interventions include sleeping medications, application of bright light, and administration of melatonin. Sleeping medications can increase the duration of daytime sleep in night-shift workers or nighttime sleep in jet-lagged individuals (9). However, sedative hypnotics are not generally recommended for chronic usage (10), because these agents become ineffective and individuals may become dependent on them. Additionally, since sedatives are, not surprisingly, associated with a decrement in performance and alertness for some time after ingestion (11), these agents have drawbacks in environments where personnel are required to respond quickly to emergency conditions.

Bright light exposure at appropriate times can shift the phase of circadian rhythms in humans (12-15). However, effects on sleep have not been documented in polysomnographic studies, and interactions of light with other interventions are unknown. Evidence shows that bright light may have a direct alerting effect that is separate from the phase-shifting effect and which also might benefit performance under conditions of circadian desynchronosis (16,17).

Melatonin, a hormone secreted by the pineal gland, shows a strong circadian rhythm with peak production during the usual nocturnal sleep period and very little production during the day. Urinary excretion of 6-sulphatoxymelatonin (6-SM) has previously been shown to be a reliable index of serum melatonin concentrations (18). Melatonin administration has been reported to shift circadian rhythms when administered at appropriate times, and it has been investigated as a therapeutic measure for treating jet lag or night-shift associated problems (19-21). The phase response curve for melatonin appears to be roughly the inverse of that for light (22). Additionally, melatonin may have sedative hypnotic actions (23,24), with associated decrements in some types of performance (24,25).

Like other physiological rhythms, the melatonin rhythm can be shifted by bright light exposure (26). Melatonin production is also acutely suppressed by bright light exposure. This suggests

that direct alerting effects of bright light may relate to melatonin suppression. However, such alerting effects are not consistently reported when melatonin is suppressed (27).

The search for better ways of improving sleep has extended into manipulation of electromagnetic fields. The idea that electromagnetic fields might alter sleep is not new (28), but it has yet to be clearly established. Recently, tests of the Symtonic Low Energy Emission Therapy (LEET) device (Symtonic SA; Renens, Switzerland), which administers very low intensity, amplitude-modulated electromagnetic fields (EMFs) intrabucally, indicate that LEET may be an effective sleep-promoting device (29-34). This device uses EMFs of a type that can induce tissue gradients around neurons similar to those seen with normal electroencephalographic (EEG) activity, and which have been shown to alter spontaneous EEG rhythms in animals. A detailed description of the LEET device has been published (34). The effects on performance or circadian rhythms of LEET[a] alone, or in combination with bright light treatment, have not been reported previously.

Some evidence indicates that EMF exposure can alter melatonin secretion (35). Thus, the mechanism of LEET's improvement of sleep might relate to alterations in the amount of melatonin secretion, or the melatonin circadian rhythm. Work in animals indicates that the phase-shifting effects of light can interact with other phase-shifting interventions (36). So, if LEET does have phase-shifting activity, it might alter the phase-shifting effects of bright light.

The purpose of this study was to examine the effects of timed bright light exposure and LEET therapy, separately and together, after a 10-hr shift of the work/rest cycle. Performance was examined with an extensive cognitive performance assessment battery (PAB), sleep was studied by polysomnographic recording,[b] and phase shifting of physiological circadian rhythms was evaluated by recording core body temperature and urinary 6-SM excretion.

METHODS

Subjects

Nonsmoking male volunteers who had no history of sleep disorders who followed a normal nighttime sleep pattern were assigned to one of four groups, as shown in Table 1. There was no significant difference between the ages of the subjects in the different groups.

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[a]The pattern of electromagnetic impulses provided by the device used in this study was different from that which has been used to treat insomnia. The pattern was specifically tailored to the purposes of the experiment (i.e., promotion of sleep during the daytime).

[b] Sleep data have been reported elsewhere.[37]

Table 1. - Experimental Groups

Group	LEET	Light	N	Age ± SD
Control	inactive	dim red	10	25.2 ± 7.7
LEET	active	dim red	12	24.8 ± 7.9
Light	inactive	bright white	12	22.5 ± 3.5
Light/LEET	active	bright white	11	23.4 ± 4.1

Procedures

The study was double-blind with regard to LEET. It was not possible to create blind conditions for the light treatment. However, subjects were aware only that red and white light were being compared. All subjects participating simultaneously were matched for light treatment. Subjects did not know that the white light was brighter than the red, so no placebo effect in favor of the bright light condition was expected.

To avoid caffeine withdrawal symptoms (38), heavy caffeine users were excluded and subjects who regularly drank coffee were allowed one 5-ounce cup of coffee with breakfast each day. Coffee and other stimulants (tea, caffeinated soft drinks) were otherwise not allowed during the study. No caffeine withdrawal symptoms were reported.

The experiment schedule is summarized in Table 2. Subjects remained in the laboratory from Sunday night through Friday morning. Continuous rectal temperature recordings were made from 2200 Sunday to 1600 Friday (except for showers) using Vitalog Portable Monitoring System Model PSM-8, with a Yellow Springs Temperature Probe Series 4400. Timed urine collections ("U" in Table 2) were made around the clock throughout the study. The total amount of 6-SM was measured on a sample of the pooled urine from each collection,[a] and an hourly excretion rate was calculated. Collection periods were timed so as not to interrupt sleep during either baseline or postshift periods. Collection periods were 0600-0800, 0800-1600, 1600-2200, and 2200-0600. For 20 min prior to the daytime sleep periods on Wednesday, Thursday, and Friday, subjects received either active or inactive LEET treatment.

Monday, subjects were trained in a cognitive PAB administered on 386 personal computers equipped with VGA color monitors. The next day, subjects underwent repeated cognitive testing

[a]The 6-SM measurements were performed by Elias USA, Inc., using the protocol of the Elias 6-sulphatoxymelatonin RIA kit.

Table 2.--Study Schedule

	SUN	MON	TUE	WED	THU	FRI
0000				TEST	TEST	TEST
0030				VS BREAK	VS BREAK	VS BREAK
0100				TEST	TEST	TEST
0130						
0200				BREAK	BREAK	BREAK
0230						
0300						
0330						
0400						
0430				VS DINNER	VS DINNER	VS DINNER
0500						
0530						
0600		WAKE U	WAKE U	BREAK U	BREAK U	BREAK U
0630		SHOWER	SHOWER			
0700		BREAKFAST	BREAKFAST			
0730				LEET	LEET	LEET
0800		TRAIN U	TEST U	SLEEP U	SLEEP U	SLEEP U
0830						
0900		VS BREAK	VS BREAK			
0930						
1000		TRAIN	TEST			
1030						
1100		BREAK	BREAK			
1130						
1200		TRAIN	TEST			
1230						
1300		VS LUNCH	VS LUNCH			
1330						
1400		BREAK	TEST			
1430						
1500			BREAK			
1530						
1600		U	TEST U	WAKE U	WAKE U	WAKE U
1630				SHOWER	SHOWER	SHOWER
1700		VS DINNER	VS DINNER	VS BREAKFAST	VS BREAKFAST	BREAKFAST
1730						
1800		BREAK	TEST	TEST	TEST	
1830						
1900			BREAK	BREAK	BREAK	
1930						
2000	CHECK-IN	FULL EEG HOOKUP	TEST	TEST	TEST	
2030						
2100	PARTIAL EEG HOOKUP	VS BREAK	VS BREAK U	VS BREAK U	VS BREAK U	
2130						
2200	SLEEP	SLEEP U	TEST	TEST	TEST	
2230						
2300			SNACK	LUNCH	LUNCH	
2330						

U = Urine collection. *VS* = Vital Signs. TRAIN = Training on cognitive performance tests. TEST = Cognitive performance testing. Cognitive performance data to be reported elsewhere.

during one 9-hr day shift (0800-1700), with 5 PAB sessions at 2-hr intervals. During the three subsequent nights, they were tested on the PAB for a 9-hr night shift (1800-0300). Most of the PAB tasks were from the Walter Reed PAB (39). Descriptions of the PAB tasks are provided in the Appendix.

From 2200 to 0200 during each nighttime work period, subjects were exposed to either bright-white or dim-red light. Light boxes (Brite Lite III; Apollo Light Systems) were located just above the computer monitors (midpoint of light box 24 inches above table surface), in or almost in the field of direct vision as the subjects viewed the monitors. For bright light, the boxes contained two tubes and had a transparent cover. For dim light, a single tube and a red cover were used. For the groups that received bright light, additional light was provided by overhead lights. Overhead lights were off during the 2200-0200 time period for the dim light groups. Lux measures at eye level were 3,500 to 4,300 lux for the bright light and 200 to 300 lux for the dim light. At other times, background lighting was less than 550 lux from overhead lights (varying depending on where the subjects were in the lab and what they did on their breaks).

Analysis Methods

Performance - One-way analyses of variance (ANOVA) were done for each baseline performance measure (mean of sessions from Tuesday 0800 to 1700) to see if any group differences existed prior to the interventions (light or LEET). For performance measures not showing significant baseline differences, a multivariate analysis of variance (MANOVA) was done, with Light and LEET as the between-group factors, and Day (average of five sessions) as the within-group factor. For the three measures (Four-Choice throughput [TP; number correct per unit of response time; a combined accuracy/speed measure] and reaction time [RT], and Word Memory percent correct [PC]) showing baseline differences, multivariate analysis of covariance (MANCOVA) was done with the baseline value as the covariate (adjusted out of subsequent day means). To try to discriminate direct-alerting from phase-shifting effects of light, the mean value for each measure during sessions where bright light exposure occurred and the mean for sessions without bright light exposure were calculated, and a Light by LEET by Day by Exposure analysis was performed.

Missing data were replaced by using the mean of the preceding and subsequent sessions. Data replacement never involved more than one session of any task, and more than 80% of subjects had no missing sessions.

Temperature and melatonin - Hourly average temperatures were computed.[a] Due to equipment problems, only 31 subjects had complete temperature values (9 Control subjects, 7 Light subjects, 8 LEET subjects, and 7 Light/LEET subjects). Of these, one subject in the Light group showed a very abnormal temperature rhythm at baseline (e.g., his first temperature peak occurred at 0100) and was therefore excluded from the temperature and melatonin analyses.

The hourly excretion of 6-SM was calculated for each collection period. For cosinor analyses (40), because of the dramatic intersubject variability in the amounts of 6-SM excreted, the 6-SM data were expressed as log base 10 (ng/hr) and the midpoint of the collection period was treated as the sample time. Four Light subjects and 3 Control subjects were missing one or two 6-SM values from the 0600 to 0800 sampling period due to inability to void or a missed sample. In these cases, the mean 6-SM level from the urine collections before and after the missed collection were used to estimate the missing value. Excluding these 7 subjects did not the alter significant findings.

For each subject, both an overall cosinor analysis (Total) and separate cosinor analyses on the Pre-exposure (Pre; before Tuesday 2200), Early Exposure (2200 Tuesday to 0200 Thursday), and Late Exposure (0300 Thursday to 1700 Friday) data were performed to detect the acrophase (hour of peak value), amplitude (height of wave), and percent of variance accounted for (R^2) by the 24-hr cyclicity.

RESULTS

Melatonin

No significant differences between the groups in mean daily 6-SM excretion were present at baseline (Samples 3-6: Light = 2.34 $\pm$ .38, Light/LEET = 2.39 $\pm$ .47, Control = 2.38 $\pm$ .40, LEET = 2.36 $\pm$ .41 $\log_{10}$[ng/hr]). The R^2 of the best fitting 24-hr cosinor fit was transformed into a Fisher's z. A one-way ANOVA on the Fisher's z data from the Pre-exposure period showed no significant differences between the four groups ($F[3,42] = 1.54$, $p \leq .21$). A two-way repeated-measure ANOVA across the Pre, Early, and Late periods showed no significant Light or LEET effects, but R^2 was higher in the Late ($R^2 = .92$) than in the Pre ($R^2 = .82$) or Early ($R^2 = .81$) phases, indicating that 24-hr cyclicity was most pronounced at the end of the study.

[a]Temperatures below 35°C or above 40°C were presumed erroneous and excluded from the calculation.

Amplitude and phase cosinor results were used to compute the arctangent as shown below (41,42):

arctan = mean [amp * sin(phase)] / mean [amp * cos(phase)]

Acrophase angles from the arctangent analysis are shown in Table 3, and amplitude results are shown in Table 4. The data in Table 3 show that the subjects who received bright light showed a mean phase delay of 52° (about 3.5 hr) in the Early Exposure phase, as compared to 23° (about 1.5 hr) in the dim light subjects. The additional shift in the Late Exposure period is also slightly larger in bright light-exposed subjects (30°, 2 hr) than in dim-light exposed (19°, 1.25 hr). MANOVA, with Light and LEET as between subject factors, showed a significant Light by Stage of Experiment (Pre, Early, and Late periods) effect ($F[2,40] = 3.44$, $p \leq .02$), with the groups that received bright white light showing a greater phase delay in both the Early and Late Exposure periods than those who received dim red light (Early: $T^2 = 8.71$, $F[2,43] = 4.25$, $p \leq .02$; Late: $T^2 = 8.45$, $F[2,43] = 4.37$, $p \leq .02$). The data in Table 4 indicate poor cyclicity of the Pre-exposure data (95% confidence interval of amplitude overlaps zero). However, clear cyclicity is evident in the Early and Late exposure data, and nothing suggests a baseline difference between the groups exposed to bright light and those exposed to dim light. Figure 1 shows the best fitting 24-hr cosinor curves for the Pre and Late exposure data for subjects who received dim and bright light.

Fig 1. -- Best fitting 24-hr cosinors Pre and Late exposure for bright white and dim red groups

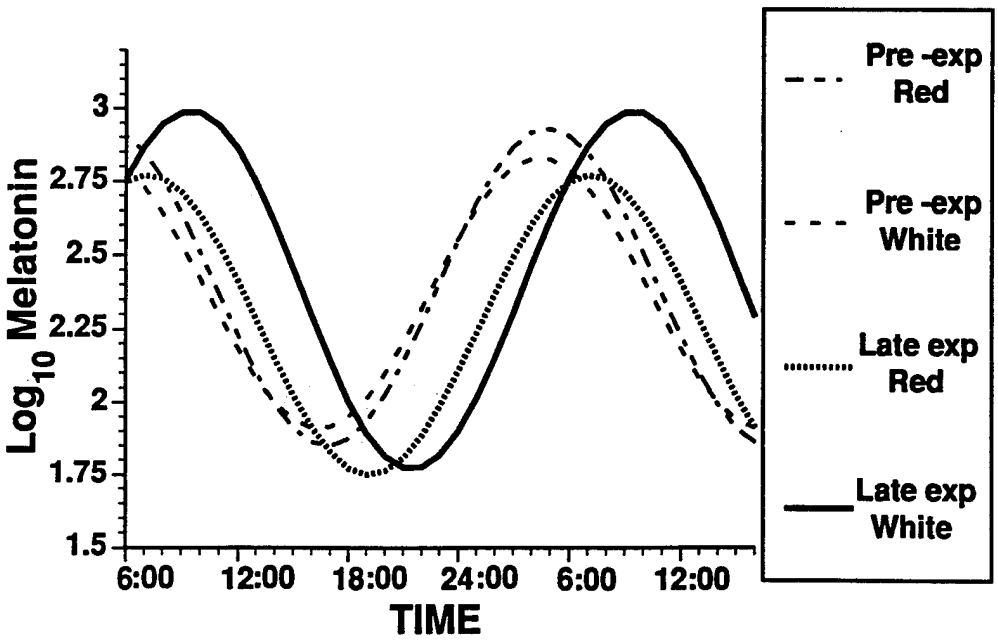


Table 3. - Acrophase Angles (95% confidence interval)

EXPOSURE / GROUP	PRE	EARLY	LATE
LIGHT	-54 (-179 to 74)	-114 (-147 to -81)	-160 (-172 to -148)
LIGHT/LEET	-70 (-94 to -46)	-114 (-154 to -74)	-135 (-153 to -113)
MEAN BRIGHT	-62 (-136 to -12)	-114 (-149 to -82)	-144 (-158 to -123)
CONTROL	-52 (-246 to 185)	-90 (-115 to -65)	-111 (-122 to -101)
LEET	-72 (-134 to -10)	-84 (-101 to -67)	-103 (-136 to -70)
MEAN DIM	-64 (-159 to 41)	-87 (-101 to -73)	-106 (-127 to -88)

Table 4. - Amplitude (95% confidence interval)

EXPOSURE / GROUP	PRE	EARLY	LATE
LIGHT	0.56 (0.00-1.11)	0.56 (0.21-0.78)	0.74 (0.53-0.77)
LIGHT/LEET	0.52 (0.19-0.66)	0.51 (0.18-0.79)	0.60 (0.38-0.80)
MEAN BRIGHT	0.25 (-0.01-0.49)	0.49 (0.20-0.78)	0.60 (0.42-0.78)
CONTROL	0.43 (0.00-0.99)	0.50 (0.18-0.57)	0.73 (0.51-0.62)
LEET	0.80 (0.00-1.11)	0.74 (0.34-0.85)	0.59 (0.16-0.78)
MEAN DIM	0.35 (0.00-0.96)	0.49 (0.30-0.68)	0.51 (0.34-0.68)

Temperature

The fit (R^2) of the 24-hr cosinor analyses of the temperature data did not differ between groups either in the Pre-Exposure period ($F[3,30] = .42$, $p \leq .74$) or across the entire study ($F[3,30] = .61$, $p \leq .61$). A significant acrophase shift of about 5 hr occurred ($F[2,31] = 6.62$, $p < .001$); however, almost all of the shift occurred between the Pre-Exposure and Early Exposure periods ($T^2 = 24.28$, $F[2,33] = 11.78$, $p < .001$), with no significant further shift between the Early and Late Exposure periods. No differences were present between the groups in amount of acrophase shift.

Baseline Performance

Baseline data analyses showed significant main effects of Group for Four-Choice TP ($F[3,40] = 3.01$, $p \leq .04$) and RT ($F[3,40] = 2.71$, $p \leq .05$), and Word Memory PC ($F[3,39] = 3.20$, $p \leq .03$). On Tukey's HSD post-hoc testing, the Light group did better than the Light/LEET group for Word Memory PC and better than the LEET group on Four-Choice TP, but no group comparison was significant for Four-Choice RT. MANCOVA with the baseline score as a covariate was used rather than MANOVA for further analyses on Four-Choice TP and RT, and Word Memory PC to adjust for initial differences.

Postshift Performance

The performance data are shown in Table 5. Intervention-related findings from the overall analyses are shown in Table 6, and measures with significant intervention-related effects in those analyses are plotted in Figures 2-7.

Addition TP showed Light by Day and LEET by Day interactions (Figures 2 and 3, respectively), with a trend for a main effect for Light. Bright light-exposed subjects always performed better than dim light-exposed subjects. Post-hoc testing showed no significant differences between bright light-exposed and dim light-exposed subjects for any day, although the difference approached significance the second night after the shift ($t[42] = 1.91$, $p \leq .06$). LEET-exposed subjects always performed better than nonexposed, but none of the individual comparisons by day approached significance at $p < 0.1$.

Addition PC showed a Light by Day effect (Figure 4) and a trend for a main effect for LEET. Bright light-exposed subjects always performed better than did dim light-exposed subjects. The group difference approached significance the first night after the shift ($t[42] = 1.86$, $p \leq .07$).

Table 5. - Cognitive Performance

	DAY 1 (BASELINE)				DAY 2				DAY 3				DAY 4			
	L/L	LIGHT	LEET	CON	L/L	LIGHT	LEET	CON	L/L	LIGHT	LEET	CON	L/L	LIGHT	LEET	CON
ADD TP	**35.9**	**37.3**	**35.1**	**30.2**	**36.6**	**34.9**	**33.7**	**26.1**	**41.1**	**39.9**	**36.5**	**28.4**	**42.1**	**41.1**	**37.5**	**31.6**
	15.4	8.7	10.5	9.5	15.1	7.8	11.5	8.4	17.6	10.7	11.0	8.0	19.2	11.2	12.5	9.5
RT	**17.3**	**14.7**	**16.3**	**18.3**	**17.4**	**15.6**	**17.4**	**20.0**	**15.4**	**14.3**	**16.0**	**18.3**	**14.6**	**13.5**	**15.2**	**16.8**
	6.7	3.0	4.7	5.4	6.9	3.0	6.1	6.3	6.9	3.5	5.3	4.0	6.6	3.7	5.1	4.0
PC	**91.3**	**88.8**	**90.6**	**86.5**	**92.7**	**89.5**	**89.8**	**82.2**	**92.0**	**89.1**	**89.9**	**83.5**	**89.8**	**88.4**	**88.5**	**85.4**
	12.8	6.1	5.7	8.6	11.4	5.5	6.0	8.2	6.4	5.0	5.6	7.0	9.6	4.9	5.8	7.9
WOR RT	**.80**	**.71**	**.79**	**.77**	**.71**	**.66**	**.78**	**.77**	**.68**	**.68**	**.77**	**.76**	**.64**	**.67**	**.75**	**.70**
	.10	.12	.15	.12	.10	.14	.16	.11	.10	.14	.15	.14	.11	.16	.16	.11
PC	**83.4**	**88.1**	**82.9**	**82.3**	**82.9**	**87.1**	**80.5**	**77.4**	**83.4**	**85.7**	**82.9**	**81.2**	**81.7**	**85.7**	**84.3**	**82.0**
	6.0	5.5	5.3	4.5	6.7	8.7	6.8	8.7	8.0	8.6	7.0	5.5	11.3	9.4	7.6	6.0
CRT TP	**34.6**	**35.9**	**34.9**	**36.7**	**34.8**	**35.9**	**33.0**	**34.2**	**34.9**	**35.7**	**32.7**	**33.9**	**35.0**	**35.4**	**33.4**	**33.8**
	1.0	1.2	1.7	1.8	1.1	.9	3.5	1.8	2.1	1.5	2.8	2.3	1.4	1.2	2.7	3.3
RT	**.37**	**.39**	**.38**	**.36**	**.38**	**.41**	**.41**	**.39**	**.36**	**.40**	**.40**	**.38**	**.37**	**.39**	**.40**	**.37**
	.07	.07	.07	.05	.05	.08	.08	.07	.05	.07	.08	.07	.07	.06	.07	.06
PC	**89.6**	**89.2**	**83.6**	**84.8**	**89.7**	**91.3**	**85.2**	**87.6**	**88.9**	**92.1**	**87.0**	**89.4**	**90.4**	**91.4**	**86.8**	**90.4**
	5.0	5.3	8.4	7.8	7.2	3.9	8.2	5.7	11.1	2.1	7.1	6.1	7.5	4.0	6.9	6.3
SRT	**.19**	**.23**	**.21**	**.21**	**.18**	**.24**	**.24**	**.22**	**.17**	**.23**	**.23**	**.21**	**.17**	**.23**	**.21**	**.21**
	.06	.07	.05	.06	.05	.06	.06	.05	.03	.07	.05	.04	.05	.07	.07	.04
SYN	**1603**	**1888**	**1673**	**1582**	**1779**	**1899**	**1779**	**1724**	**2074**	**2202**	**1943**	**1997**	**2189**	**2313**	**2097**	**2174**
	414	188	457	394	349	193	470	434	367	284	533	397	389	296	590	435
LOG RT	**9.38**	**6.44**	**8.21**	**8.88**	**10.0**	**5.83**	**8.04**	**10.4**	**6.34**	**5.08**	**7.73**	**7.70**	**5.95**	**4.54**	**6.40**	**6.56**
	2.88	1.69	4.71	3.62	7.47	1.43	4.43	6.43	2.20	1.69	2.20	2.63	1.54	1.04	3.48	2.23
PC	**95.4**	**94.6**	**93.5**	**88.4**	**95.9**	**96.5**	**93.4**	**91.7**	**95.0**	**97.7**	**94.8**	**94.0**	**95.2**	**97.9**	**94.9**	**95.7**
	4.3	3.6	8.0	9.5	4.4	2.7	7.2	7.3	8.8	1.3	5.2	3.3	7.9	1.4	5.2	1.9
4-C TP	**453**	**466**	**433**	**447**	**459**	**461**	**427**	**440**	**469**	**470**	**435**	**450**	**469**	**473**	**444**	**457**
	23	15	39	31	15	16	46	35	14	14	41	35	16	16	35	39
RT	**.45**	**.41**	**.53**	**.48**	**.43**	**.42**	**.56**	**.50**	**.40**	**.40**	**.53**	**.47**	**.40**	**.39**	**.49**	**.44**
	.87	.05	.14	.12	.05	.05	.18	.14	.04	.04	.16	.14	.05	.05	.12	.15
PC	**99.5**	**99.4**	**99.5**	**99.4**	**99.6**	**99.3**	**99.5**	**99.5**	**99.4**	**99.6**	**99.7**	**99.7**	**99.6**	**99.5**	**99.2**	**99.5**
	.6	.4	.3	1.0	.3	.5	.4	.4	1.0	.2	.2	.2	.4	.4	1.5	.5
TAP	**.10**	**.33**	**.21**	**.30**	**.55**	**.16**	**.30**	**.40**	**.13**	**.11**	**.42**	**.07**	**.16**	**.31**	**.40**	**.49**
	.16	.37	.38	.38	1.61	.25	.34	.36	.21	.16	.56	.14	.25	.52	.46	.71
VAS	**60.2**	**58.5**	**68.6**	**52.6**	**57.4**	**52.0**	**56.1**	**47.2**	**64.5**	**66.8**	**64.6**	**53.0**	**58.8**	**55.5**	**61.4**	**52.0**
	15.6	17.1	19.4	11.5	18.5	14.5	17.7	10.5	19.4	16.0	17.6	10.2	23.4	16.0	16.4	12.8

CON = Control, ADD = Addition, TP = Throughput, RT = Reaction Time, PC = Percent Correct, SD = Standard Deviation, WOR = Word Memory, CRT = Complex Reaction Time, SRT = Simple Reaction Time, SYN = Synwork, LOG = Logic, 4-C = Four-Choice Reaction Time, TAP = Tapping task, VAS = Variable Analog Scale of mood. **Bolded** numbers = means, unbolded = SD's.

Table 6. - Intervention-Related Effects in the Overall Performance Analyses

FACTORS TASK DF	LIGHT (1,40)	LEET (1,40)	LIGHT LEET (1,40)	LIGHT DAY (3,38)	LEET DAY (3,38)	LIGHT LEET DAY (3,38)
ADD TP	.085 (3.12)			**.03** (3.25)	**.002** (5.82)	
PC		.07 (3.46)		.02 (3.63)		
WOR PC[a]				**.03** (3.78)		
RT	.07 (3.37)			.06 (3.07)		
CRT TP	**.01** (6.68)	.09 (3.02)		**.002** (6.18)		
PC	.06 (3.77)					
SRT			.08 (3.29)			
SYN						**.03** (3.27)
LOG PC	.07 (3.37)				.07 (2.53)	
RT			.09 (3.01)			
4-C TP[a]	.08 (3.28)					
PC			.06 (2.73)			
RT[a]			.06 (3.67)			
VAS			.05 (2.83)			

DF = Degrees of Freedom, ADD = Addition, TP = Throughput, PC = Percent Correct, RT = Reaction Time, WOR = Word Memory, CRT = Complex Reaction Time, SRT = Simple Reaction Time, SYN = Synwork, LOG = Logic, 4-C = Four-Choice, VAS = Variable Analog Scale of mood. Numbers represent p values (F values). Significant p values are **bolded**, except where the p value on the univariate test was $.05<p<0.1$. Cases where the p value for the multivariate test was <.1 but the univariate p value was >0.1 have not been included.

[a]MANCOVA was used for these measures, and DF is one less than specified at the top of column.

Fig 2. -- Addition Throughput Bright vs. Dim Light

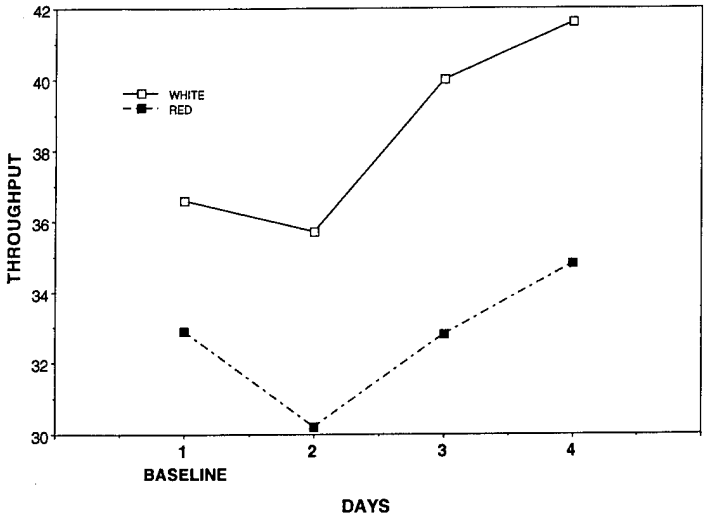


Fig 3. -- Addition Throughput LEET vs. No-LEET

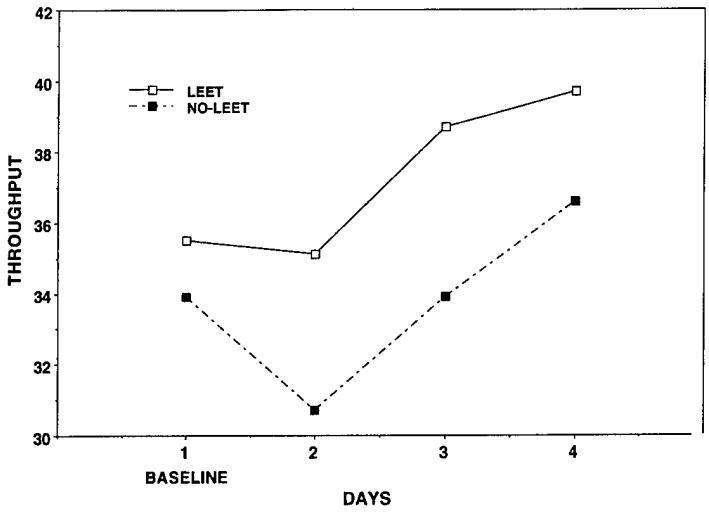


Fig 4. -- Additiion Percent Correct Bright vs. Dim Light

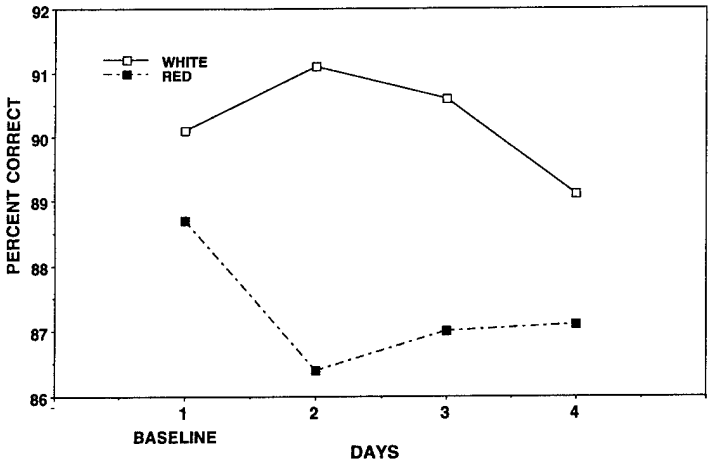


Fig 5. -- Word Memory Percent Correct Bright vs. Dim Light Adjusted for Baseline Differences

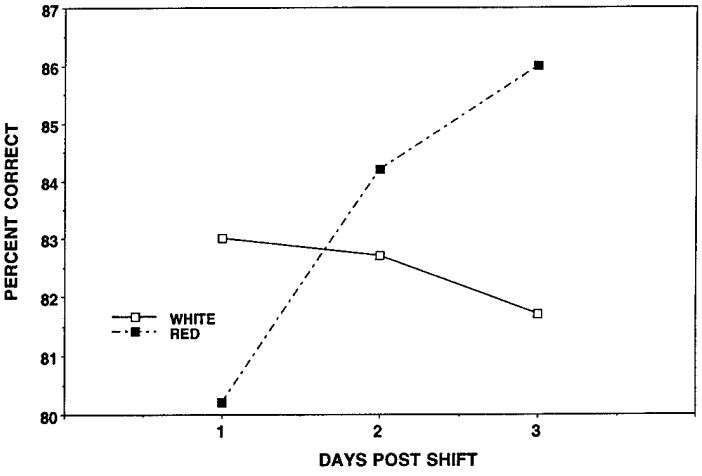


Fig 6. -- CRT Throughput Bright vs. Dim Light

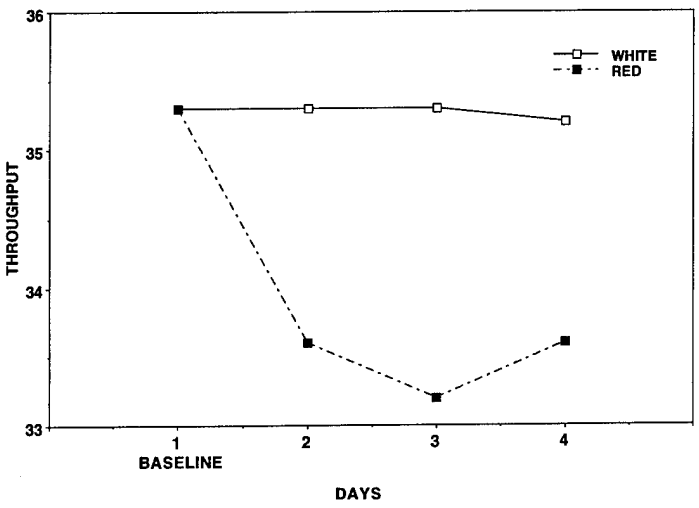
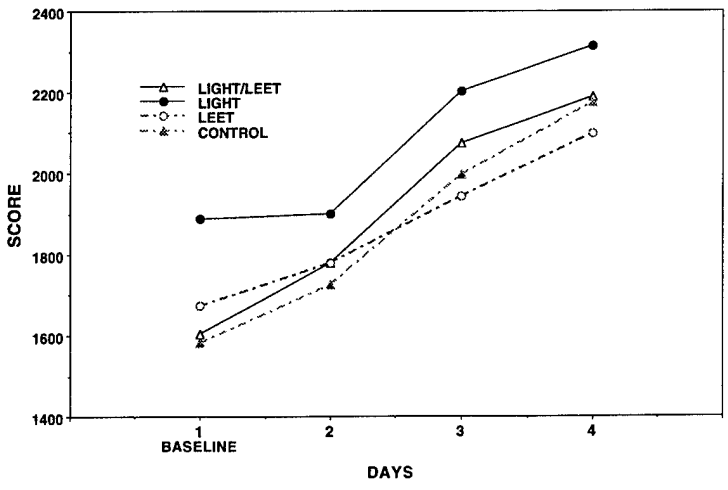


Fig 7. -- Synwork



LEET exposed subjects always performed better than did nonexposed, but the group differences were greater prior to LEET exposure (Baseline and Day 2) than after.

Word Memory PC showed a Light by Day interaction (Figure 5, the Baseline day is not included because the data have been adjusted for baseline differences). Subjects who received bright light showed a marginally higher accuracy than those who did not the first night after the shift, which approached significance at the standard level ($t[42] = 1.67$, $p \leq .10$), averaged about the same the second night, and were less accurate than the non-bright light-exposed subjects the final night ($t(42) = 2.02$, $p \leq .05$). The overall pattern is that the bright light subjects started out higher and remained at about the same level, while the dim light subjects started out lower and gradually improved.

Word Memory RT showed trends for a main effect for Light and for a Light by Day interaction. Bright light-exposed subjects were always faster than were dim light-exposed subjects, with the greatest difference the first night postshift (.69 s vs. .80 s, $p \leq .02$).

Complex Reaction Time (CRT) TP showed a main effect for Light, a Light by Day interaction (Figure 6), and a trend for a main effect for LEET. Bright light-exposed subjects performed significantly better than did dim light-exposed on all three postshift testing sessions, with the largest difference the second postshift night (Day 3). LEET exposed subjects always performed worse than did nonexposed, but group differences were as great before any LEET treatment had occurred as after. CRT PC showed a trend for a main effect for Light. Bright light-exposed subjects always showed higher accuracy than did dim light-exposed subjects. However, this difference was greatest at baseline.

Simple Reaction Time (SRT) RT showed a trend for a Light by LEET effect. The Light/LEET group tended to be faster than the other groups (overall means: Control - .22 $\pm$ .05, Light - .23 $\pm$ .06, LEET - .22 $\pm$ .05, Light/LEET - .18 $\pm$ .04). However, this was true at baseline as well (see Table 5).

The Synwork task showed a Light by LEET by Day interaction (Figure 7). The LEET group performed a little better than did the Control and Light/LEET groups at baseline, but it performed a little worse than did both these groups the last two nights. The Light group always tended to perform better than the other groups. However, this is most prominent at baseline, decreasing thereafter.

Logical Reasoning PC showed trends for a Light effect and a LEET by Day interaction. Bright light-exposed subjects always performed more accurately than did dim light-exposed subjects,

however, the difference is largest at baseline. LEET exposed subjects started out a little more accurate, but they improved less across the course of the study than did nonexposed subjects and were less accurate by the end of the study. A trend exists for a Light by LEET interaction on Logic RT. The Light group was always faster than the other groups, but this pattern is present at baseline (Table 5).

Four-Choice showed trends for a Light effect on TP and for Light by Day interactions on PC and RT. Bright light-exposed subjects showed higher TPs than did dim light-exposed the first and second nights after the shift ($p \leq .04$ and $p \leq .07$, respectively). They also showed faster RTs than did dim light-exposed those nights ($p \leq .03$ and $p \leq .06$, respectively). In contrast, they were slightly less accurate the first 2 nights postshift and slightly more accurate the final night. However, PC for all groups remained above 99% at all times.

The Visual Analog Scale for alertness showed a Light by LEET interaction. Bright light subjects started out slightly less alert at baseline, dropped less the first night after the shift, and rose much more the second night after the shift. On the last night both groups dropped to a similar level. Between-group post-hoc comparisons were not significant at any point. However, when scores were converted to change-from-baseline by subtracting the baseline score from each daily score, the bright light-exposed subjects were significantly more alert than were dim light exposed-subjects the second night after the shift ($p \leq .01$).

Results of the Light by LEET by Day by Exposure analyses did not show any evidence of bright light effects occurring predominantly or being greater during the sessions when the actual light exposure occurred. While a few significant interactions of Light and/or LEET with exposure occurred, the meaning of these interactions is obscure.

DISCUSSION

This study produced three main findings. First, bright light administered from 2200-0200 in subjects who have undergone a 10-hr phase delay of the work/rest cycle speeds up the resynchronization of the circadian rhythm of 6-SM excretion. Second, bright light improves accuracy of cognitive performance during the nighttime work periods. Third, LEET has little or no effect on either the 6-SM rhythm or cognitive performance.

Melatonin

The 6-SM data showed the expected effects of light. In the early exposure period of the study, subjects exposed to bright light phase delayed the melatonin rhythm more than twice as much as those exposed to dim light (Table 3). Both groups showed smaller additional phase shifts in the Late Exposure period of the study, but the bright light-exposed subjects still shifted more than did the dim.

Because the timing of light exposure was the same for all subjects, rather than positioned more exactly in relation to each individual's circadian phase positioning, maximal phase shifts could not be expected. Exact circadian phase can vary considerably among individuals (43,44). Also, some controversy exists about the direction of phase shift that will result with light exposure very near to the circadian nadir. For example, Tzischinsky and Lavie (45) report phase-advances with bright light exposure at times of day when Deacon and Arendt (46) and others have found it to cause phase delays. Thus, it was deemed safer to keep the bright light exposure at a moderate distance from the presumed circadian nadir (0400-0600), to avoid any chance of causing phase advances. The smaller bright light effects in the Late Exposure period of the study suggest that the conservative timing of the light plus the initial large phase shift in the Early Exposure period of the study resulted in the light falling in a relatively inactive area of the phase response curve during the Late Exposure period of the study.

It is possible some of the apparent light-related increased phase shift might be caused by direct melatonin suppression. However, since bright light exposure occurred during only the first half of the relevant urine collection period, and melatonin levels have been reported to rebound above baseline levels after a period of bright light (47), it seems unlikely that the apparent increase in phase shift is an artifact related to melatonin suppression distorting the shape of the melatonin rhythm.

Temperature

In contrast to the findings for melatonin, the temperature data did not show a phase delaying effect of Light. All groups shifted similarly. It was discovered part way through the data collection that, when subjects wished, technicians had been permitting them to engage in aerobic exercise on a treadmill in the laboratory during break periods. Thereafter, aerobic exercise was not permitted. However, since there was no record of which subjects exercised or when they did so, the masking effect of exercise-related temperature increases will have obscured the endogenous temperature rhythm to an unknown degree. The fact that light did significantly promote phase advance of the melatonin rhythm supports the possibility that the temperature data

have been obscured by masking effects, since these two measures usually show corresponding shifts (26).

Performance

Effects of Day were seen on many performance measures in the overall MANOVA/MANCOVAs. This may be due to the effects of inadvertant practice obtained by taking the test repeatedly (e.g., Figure 6). However, in other data a prominent decrement occurred during the first night-testing period, presumably related to sleep deprivation (e.g., Figures 2 and 3).

Evidence indicated the bright-light treatment affected accuracy of performance. All TP and PC measures showed at least a trend for a Light or a Light by Day effect. These findings must be qualified by the tendency for groups who received bright light to show somewhat better performance at baseline on some measures. Additionally, a large number of comparisons have been made on data from a small number of subjects. Thus, the findings must be considered preliminary. Unfortunately, combining multiple varaiables into a doubly-multivariate analysis, which might resolve some of the problems related to repeated comparisons, presents difficulties in repeated measure designs, such as the one used in this study (48).[a]

Nonetheless, the generality of the pattern is fairly compelling. For all of these measures, except Word Memory PC, subjects who received bright light performed better than those who did not. On Word Memory, subjects who received bright light were more accurate than those who did not during the first night-testing period, but they were less accurate than the dim light-exposed subjects in the final testing period (Figure 4). Since complex memory is perhaps the only type of cognitive performance that has been reported to peak around the time of the temperature nadir (49), this pattern could support phase-shifting effects of the bright light (i.e, light subjects shifting farther from their baseline phase position may have moved past the optimum phase for this type of performance).

No significant Light or Light by Day effects occurred for the RT measures. Thus, the benefits to accuracy occurred without any sacrifice of speed.

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[a]A combination analysis was attempted for the PC data. This analysis could not include the baseline data, because there were too few subjects for the degrees of freedom required. An analysis of just the postshift days was questionable because a combined analysis of the baseline day showed a significant effect for Light, with bright light-exposed subjects doing better. A combined MANCOVA correcting for the baseline differences also violated degrees of freedom requirements. A combined MANCOVA of only Day 1, adjusted for baseline differences, showed an effect of Light ($F[5,31] = 3.74$, $p = .009$) with subjects who received bright light improving accuracy the first night, while those who received dim light became less accurate. Similar MANCOVAs for Day 2 and Day 3 showed no Light or LEET effects.

The subjective alertness results suggest bright light also decreased problems with loss of alertness the first 2 nights after the shift. When the slight baseline differences were corrected for, bright light-exposed subjects were significantly more alert during the second night. However, since this Light by Day interaction is significant only on the multivariate test (univariate: $F = 1.74$, $p = .16$), bright light effects on this measure are dubious.

As was discussed previously, the timing of bright light in this study was not determined by each individual's baseline circadian rhythms. While more dramatic effects on performance might have been achieved with more exact timing of the administration of bright light for each individual, the present findings are probably more consistent with "real world" applications, given that determination of circadian phase position is a difficult and time-consuming procedure.

Interestingly, there was little evidence of LEET affecting performance. Only one significant LEET by Day interaction occurred, and this, as well as the three trends for LEET or LEET by Day effects on other measures, appear questionable upon examination. In relation to the LEET by Day interaction on Addition TP and the trends for LEET effects on Addition PC and CRT TP, the largest differences between subjects treated with active and inactive LEET occurred during the first night-testing period. However, since the first LEET exposure occurred after this testing period, these cannot be effects of LEET. The other trend was for a LEET by Day interaction on Logic PC with subjects who did not receive LEET improving progressively across the night-testing sessions (from 94 to 97%), while LEET exposed subjects showed no change (95%).

Synwork showed a Light by LEET by Day interaction (Figure 7). The LEET group performed better than did the Light/LEET and Control groups at baseline, but worse during the last two nights of the study. The LEET vs. Control comparison might be interpreted as suggesting a negative effect of LEET on performance or on learning, but since a similar pattern is not seen in the Light/LEET vs. Light comparison, such an interpretation seems doubtful.

It was presumed that if LEET affected performance it would do so secondarily to a decrease in the sleep disruption caused by the phase shift. Analysis of the sleep data indicated only a nonsignificant trend for improvement with LEET (37). So, significant performance improvement would not be expected. Our data also do not support a direct impairment of performance by LEET, as has been reported with sedative hypnotic drugs (50). In summary, the data provide no evidence that LEET promoted phase shifting or altered performance.

CONCLUSION

After a 10-hr phase delay in the work/rest schedule, melatonin data (6-SM excretion in the urine) indicate that bright light exposure from 2200-0200 increases the phase delay seen in this circadian rhythm in the 3 days after the work/rest schedule shift. Temperature data appear to have been obscured by activity level-related masking effects. The bright light treatment shows evidence of improving accuracy on a broad range of cognitive performance, without compensatory decreases in speed. One task showed decreased accuracy, possibly because the function tested has a performance rhythm out of phase with most other types of cognitive performance. The cognitive performance findings are most consistent with phase shifting effects of bright light rather than direct alerting effects, since there was no evidence of greater effects during the actual light exposure periods than at other times. LEET administration before the daytime sleep periods showed little evidence of affecting either performance or circadian rhythms.

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APPENDIX: PAB TASKS

The PAB was composed of the following tasks:

1. **Two-Digit Column Addition Task** (Addition, Walter Reed PAB task). This task measures the ability to add five two-digit numbers arranged in a column. The task is dependent on ability to remember the sum of the right-most digits. The subject types in the answer on the numeric keypad. Measures: percent correct (PC), reaction time (RT), and throughput (TP; number correct per unit of response time; a combined accuracy/speed measure). Task duration is 10 min.

2. **Four-Choice Serial Reaction Time Task** (Four-Choice, Walter Reed task). This task measures ability to track visual stimuli. A star is displayed in one of the four quadrants of the screen. The subject must press a key on the keyboard whose position corresponds to the quadrant the star is in. Each stimulus is displayed until the subject responds, after which the next stimulus is immediately displayed. Measures: PC, RT, and TP. Task duration is 11 min.

3. **Variable Difficulty Logical Reasoning Task** (Logic, a variation of a Walter Reed PAB task). In this task, a letter sequence is displayed on the screen at the same time as logical statement(s) about the order of the letters. There are 30 problems, 10 each at three levels of difficulty (a single logical statement combined with "AB" or "BA"; two statements combined with "A," "B," and "C" in any order; and three statements combined with "A," "B," "C," and "D" in any order). If all statements accurately describe the letter sequence, subjects type "T" for "true." If any statement does not describe the letter sequence, subjects type a "U" for "untrue." An example of this task is:

   CAB

   A does not precede B

   C does not follow B.

   Because the first statement is incorrect and the second one is correct, the answer to this example is to press the "U" key. Measures: PC and RT. Completing the 30 problems

usually takes subjects about 5 min.

4. **Tapping Task**. This task measures ability to sustain attention to an easy task. The task requires tapping a key at a rate of once per second. "Lapses" in tapping are scored when subjects pause for more than 3 s between taps. When subjects pause for more than 10 s, the computer beeps, reminding them to resume tapping. Increase in numbers of lapses previously has been observed to correlate with shorter sleep latency as measured by the Multiple Sleep Latency Test (MSLT; Johnson, Spinweber, & Gomez, 1990). Thus, the tapping task measures both slowing due to sleep loss and objective sleepiness. Measure: lapses. Task duration is 5 min.

5. **Simple and Complex Reaction Time Task** (SRT and CRT). This task has two parts. In the SRT part, each trial starts with a blue square appearing in the center of the screen. Subjects must depress a response key on the mouse and hold it until, after a variable interval, the square turns green, when the key must be released. In the CRT part, the trials start the same but the second color may be either green or red. When the square turns green, the subjects must release the key as quickly as possible. For red signals the subjects must keep the key depressed for 1 s before releasing. Measures: only RT for SRT; PC, RT, and TP for CRT. The two parts of the task each last 5 min.

6. **Word Memory Task**. On each trial, a list of 20 words is displayed for 20 s. Subsequently, 20 words (10 from the list, and 10 not from the list) are presented singly and in random order. The subjects must respond "T" if they think the word was in the list and "U" if it was not. The task consists of administration of six sessions. Measures: PC and RT. Duration is 10 min.

7. **Synthetic Work Task (Synwork).** This is composed of four different tasks presented simultaneously in the four quadrants of the screen. The subject must learn to maximize his overall score by balancing time among the tasks. The components were selected to provide a generic, office-type environment. All input is via a standard mouse, permitting the subject to concentrate on the information on the screen, and eliminating the distraction of a keyboard or variability related to typing skills. Measure: A single score summarizes the performance on all four component tasks. Task duration is 15 min. The component tasks are:

   a. Sternberg Memory Task -- A list of 6 random letters is displayed at the top of the window for 5 s. Clicking the mouse on the RETRIEVE LIST box at any time redisplays the list for another 5 s. A random letter is displayed in the center of the window every 20 s. The subject responds by clicking the mouse in the YES or the NO box at the bottom of the screen to indicate whether the letter is included in the list. Ten points are awarded for each correct response and deducted for each error.

   b. Arithmetic Task -- Two randomly selected numbers less than 1,000 are presented, with the answer 0000. The subject adjusts the answer by clicking on "+" and "-" boxes below each character of the answer. Clicking the DONE box at the bottom of the window causes a new problem to be presented. Ten points are awarded for each correct response and deducted for each error.

   c. Visual Monitoring Task -- A pointer moves from the center of a graduated scale toward either end at a fixed rate. Clicking the mouse on the RESET box at the top of the window resets the pointer to the center. The subject must prevent the pointer from reaching either end of the scale. Points awarded for each reset are proportional to the distance of the pointer from the center (i.e., 10 points for most distant 10%, 9 for next most distant 10%, and

so on). Ten points are deducted for each second the pointer is at either end of the scale.

d. Auditory Monitoring Task -- A 5-s tone of either low or high frequency is sounded periodically. The subject is instructed to click the HIGH TONE REPORT box at the top of the window following a high tone. High tones occur 20% of the time. A correct response given within the time limit accrues 10 points. All other responses result in the deduction of 10 points.

8. **Visual Analog Scale (VAS).** This is a measure of subjective sleepiness. The VAS test consists of positioning a marker on a line running between "VERY SLEEPY" and "VERY ALERT."

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13. ABSTRACT *(Maximum 200 words)*

Circadian desynchronosis caused by shiftwork or jet lag can have detrimental effects on alertness and performance, which could impair productivity and safety. It can also disturb sleep, which may compound subsequent performance problems. This study examined the effects of timed bright light exposure (2200-0200 each night) and Low Energy Emission Therapy (LEET), separately and together, after a 10-hr shift of the work/rest cycle. Bright-light exposure increased the phase delay seen in the circadian rhythm of melatonin in the 3 days after the work/rest schedule shift. It also shows evidence of improving accuracy on a broad range of cognitive performance, probably due to phase shifting, rather than direct alerting, effects of bright light. LEET administration before the daytime sleep periods showed little evidence of affecting either performance or circadian rhythms.

14. SUBJECT TERMS
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